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particular gene if it matched the ORF or the region 500 bp 3' of the ORF (locus names, gene names and ORF chromosomal coordinates were obtained from Stanford yeast genome ftp site, and ORF descriptions were obtained from MIPS www site on August 14, 1996. ORFs were considered genes with known functions if they were associated with a three letter gene name, while ORFs without such designations were considered uncharacterized.

At page 24, before "Additional NORFs" insert --Table 4--.

### Remarks

#### The Amendments

Claim 32 is amended to recite "an open reading frame of a *Saccharomyces cerevisiae* genome, wherein the *Saccharomyces cerevisiae* genome is shown in SEQ ID NOS:12,204-12,219" and that the open reading frame comprises the recited SAGE tag. The specification supports reciting a *Saccharomyces cerevisiae* genome at page 17, line 18: "The source of transcripts for all experiments was *S. cerevisiae* strain YPH499 . . ." The particular nucleotide sequence of the *Saccharomyces cerevisiae* genome shown in SEQ ID NOS:12,204-12,219 is supported at page 19, lines 28-31: "... we used 14 bp of SAGE tags (i.e. the *Nla*III site plus the adjacent 10 bp) to search the yeast genome directly (yeast genome sequence obtained from the Stanford yeast genome ftp site on August 7, 1996)." The nucleotide sequences shown in SEQ ID NOS:12,204-12,219 were obtained from the Stanford yeast genome ftp website on August 7, 1996 (see the accompanying declaration of Dr. Victor Velculescu, submitted in parent application Serial No. 09/012,031 on March 7, 2000). The recitation "open reading frame" is supported at page 6, lines 20-21: "New genes termed NORFs (not previously assigned open reading frames) have been found."

Claims 33, 34, and 43 are similarly amended to conform to the amendments made to claim 32, on which they depend.

Claim 32 also is amended to recite that the array of probes on the solid support is "for detecting gene expression." The specification supports this amendment at page 8, line 29, to page 9, line 2: "More preferably [the probes] are present on an array so that multiple probes can simultaneously hybridize to a single biological sample. The probes can be spotted onto the array or synthesized *in situ* on the array. See Lockart et al., **Nature Biotechnology**, Vol. 14, December 1996, 'Expression monitoring by hybridization to high-density oligonucleotide arrays.'"

Claim 33 is amended to recite that the open reading frame is "differentially expressed during the cell cycle." This recitation is supported at page 6, line 14.

Claims 35, 36, and 37 are amended to recite that each probe "has a sequence which is different from each other sequence." The specification supports this amendment at page 9, lines 2-4: "A single array can contain more than 100, 500 or even 1,000 different probes in discrete locations." This amendment does not narrow the scope of claims 35, 36, or 37.

Claim 34 is amended to delete the recitation "NORF No. 1, 2, 4, 5, 6, 17, 25, and 27" and to refer to the open reading frames of these genes instead by reference to the SAGE tag each open reading frame comprises. This amendment is supported by Table 3, which correlates each NORF with a particular SAGE tag. This amendment does not narrow the scope of claim 34.

Claim 44 is reworded to clarify that "the at least one probe of each of the open reading frames comprises a SAGE tag." This amendment does not narrow the scope of claim 44.

The specification is amended to insert sequence identifiers for the sequences of the 16 yeast chromosomes provided in the formal sequence listing filed April 10, 2001. The

specification also is amended to contain the paragraph required by 37 C.F.R. § 1.52(e)(5).

References to websites in the specification have been deleted.

None of the amendments adds new matter to the specification.

#### Submission of Formal Sequence Listing

A formal sequence listing is filed today, April 10, 2001. The sequence listing is submitted on a CD-ROM only, as permitted by 37 C.F.R. § 1.812(c). Duplicate disks are submitted, as required by 37 C.F.R. § 1.52(e)(4). The specification has been amended to contain the paragraph required by 37 C.F.R. § 1.52(e)(5). The transmittal letter required by 37 C.F.R. § 1.52(e)(3)(ii) accompanies the two CD-ROMs.

The sequence listing contained on each of the submitted CD-ROMs contains those sequences explicitly disclosed in the specification, as well as the entire nucleotide sequence of each of the 16 chromosomes of the *Saccharomyces cerevisiae* genome that were available on the Stanford yeast genome ftp website referred to in the specification at page 19, lines 30-31. Inclusion of the yeast sequences was required in parent application Serial No. 09/012,031.

I believe the contents of the sequence listings on the two CD-ROMs are identical and do not add new matter to the specification.

#### The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 101

Claims 32-37, 43, and 44 stand rejected under 35 U.S.C. § 101. The Office Action alleges that the specification "does not disclose or enable a specific patentable utility for the collections of probes claimed." (Office Action at page 1, fourth paragraph). Applicants respectfully traverse this rejection.

Section 101 of 35 U.S.C. states that patentable subject matter includes "any new and useful . . . manufacture." The arrays of probes on a solid support which are recited in claims 32-37, 43, and 44 are articles of manufacture for which the following utilities are specifically disclosed in the specification:

- screening test substances for anti-fungal activity (*e.g.*, at page 2, line 26, to page 3, line 1, and at page 7, line 25, to page 8, line 2);
- screening for drugs which affect cell cycle (*e.g.*, at page 2, lines 20-25);
- identifying human genes which are involved in cell cycle progression (*e.g.*, at page 3, lines 2-9, and at page 6, lines 17-19);
- identifying homologs of the differentially expressed genes in humans and other mammals (*e.g.*, at page 6, lines 15-17, and at page 8, lines 3-15); and
- marking phases of the cell cycle (*e.g.*, at page 6, lines 14-15).

Thus, the specification discloses specific, patentable utilities for the claimed arrays of probes. Moreover, the specification enables each of the specific utilities listed above. Each of these utilities can be carried out by hybridizing two nucleotide sequences, either to monitor gene expression or to identify complementary sequences. Identification of homologs of the differentially expressed genes disclosed in the specification can be carried out using techniques that employ hybridization between two nucleotide sequences (page 8, lines 10-15). Test substances can be screened for antifungal properties by "monitoring expression of a NORF gene whose expression varies by at least 10% between any two phases of the cell cycle" (page 2, lines 28-29). Similarly, drugs that affect the cell cycle can be screened for by determining effects of the drugs on gene expression. (page 6, lines 16-17). The specification discloses probes that can be used in hybridization protocols to carry out each of these utilities (*see* page 8, lines 16-28).

Methods of using probe arrays to monitor gene expression were well known in the art at

the time the specification was filed. At the time the application was filed, for example, the art was familiar with methods of using probe arrays to monitor gene expression. Such methods include older technologies, such as "dot blot" and "slot blot" hybridization (*e.g.*, White & Bancroft, 1982, "Cytoplasmic dot hybridization. Simple analysis of relative mRNA levels in multiple small cell or tissue samples," *J. Biol. Chem.* 257, 8569; Sambrook *et al.*, MOLECULAR CLONING. A LABORATORY MANUAL, 2d ed., pages 7.53-7.57, 1989), as well as newer "microarray" technologies (*e.g.*, Chee *et al.*, 1996, "Accessing Genetic Information with High-Density DNA Arrays," *Science* 274, 610-14; DeRisi *et al.*, 1996, "Use of a cDNA microarray to analyse gene expression patterns in human cancer," *Nat. Genet.* 14, 457-60; Schena, 1996, "Genome analysis with gene expression microarrays," *Bioessays* 18, 427-31).

In addition, the specification provides a specific reference, Lockhart *et al.* (1996), to which the skilled artisan can refer for details of how to measure gene expression using a microarray. (*See* page 8, lines 19-21 of the specification). The novel aspects of the invention, *i.e.*, the NORFs and their differential expression during the yeast cell cycle, are disclosed throughout the specification (*e.g.*, at page 7, lines 8-12, page 15, lines 3-21, and Tables 3 and 4). Thus, the specification itself, as well as the general knowledge in the art, teaches one of skill in the art how to use the claimed arrays for the specific utilities disclosed.

Applicants respectfully request withdrawal of the rejection of claims 32-37, 43, and 44 under 35 U.S.C. § 101.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 112, first paragraph

Claims 32-37, 43, and 44 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written support in the specification. Applicants respectfully traverse this

rejection.

The purpose of the written description requirement is to assure that an applicant was in possession of the claimed subject matter on the date the application was filed. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1116-17 (Fed. Cir. 1991). It is well known, however, that the specification need not describe the claimed subject matter in *ipsis verbis* in order to satisfy the written description requirement. *In re Lukach*, 160 U.S.P.Q. 795, 796 (C.C.P.A. 1971).

Specifically, the Federal Circuit has repeatedly stated that whether a specification satisfies the written description requirement is a question of fact. *Tronzo v. Biomet Inc.*, 47 U.S.P.Q.2d 1829, 1832 (Fed. Cir. 1998). Moreover, because satisfaction of the written description requirement is a question of fact, "[w]hat is needed to meet the description requirement will necessarily vary depending on the nature of the invention claimed." *In re DiLeone*, 168 U.S.P.Q. 592, 593 (C.C.P.A. 1971).

Amended claims 32-37, 43, and 44 each are directed to an array of probes on a solid support. At least one of the probes must comprise at least 14 contiguous nucleotides of an open reading frame of a *Saccharomyces cerevisiae* genome comprising a particular SAGE tag. The present specification contains a sufficient written description of the claimed invention, as supported by the following facts.

The specification teaches that the entire sequence of the *Saccharomyces cerevisiae* genome was known before the application was filed and provides a reference disclosing this sequence (Goffeau *et al.*, cited at page 3, lines 28-29, of Serial No. 09/012,031, which is incorporated by reference in the present specification). Within the *Saccharomyces cerevisiae* genome, the specification teaches that the recited open reading frames (NORFs) "are uniquely identified by their SAGE tags" (page 6, lines 20-21). That unique identification is provided

because each SAGE tag, together with the adjacent NlaIII site, "matche[s] the ORF or the region 500 bp 3' of the ORF" (page 19, line 28, to page 20, line 3).

The SAGE tags themselves are disclosed in Tables 3, 4, and 6. Tables 3, 4, and 6 also disclose the chromosome on which each of the newly identified ORFs is located, as well as the position of the identifying SAGE tag on the chromosome ("tag position") and the size of the open reading frame (ORF) in which each SAGE tag is located. The specification also teaches that the SAGE tags are located within or less than 250 basepairs 3' of a NORF gene (for example, at page 5, lines 18-24). As disclosed in the specification, the yeast ORF chromosomal coordinates were obtained from the Stanford yeast genome ftp site on August 7, 1996; the sequence listing accompanying this amendment provides the identical *Saccharomyces cerevisiae* sequence that was available at the Stanford website on August 7, 1996. To identify the precise open reading frame corresponding to NORF1, for example, one would only need to refer to the publicly available information regarding the yeast genome and to locate the 198 bp ORF located at tag position 149450 on chromosome 4, located less than 250 bp 5' of the SAGE tag shown in SEQ ID NO:1. The nucleotide sequence of the NORF1 open reading frame is then easily ascertained.

The law requires that the specification be considered as a whole when determining whether it describes a particular invention. *In re Wright*, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989). The present specification provides a unique identifier for each expressed coding sequence recited in claims 32-37, 43, and 44 (the SAGE tag), as well as a sufficient positional and descriptive information to determine the nucleotide sequence of each recited open reading frame (NORF). Considering the present specification as a whole, it is clear that the present specification is more than adequate to satisfy the written description requirement of 35 U.S.C. §

112, first paragraph.

Applicants respectfully request withdrawal of this rejection of claims 32-37, 43, and 44 under 35 U.S.C. § 112, first paragraph.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 112, second paragraph

Claims 32-37, 43, and 44 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse this rejection and address each of the assertions in the Office Action below.

(a) and (g) The recitation "comprises at least 14 contiguous nucleotides of a NORF gene comprising a SAGE tag as shown in SEQ ID NOS:67-811" in claim 32 is said to be vague, indefinite, and incomplete, because the NORF genes themselves are not disclosed in the specification. The claims also are said to be incomplete because no particular organism or genome is recited in the claims. The same objections are made to the recitation "comprises at least one probe comprising at least 14 contiguous nucleotides of each of the NORF genes identified by the SAGE tags shown in SEQ ID NOS:67-811" in claim 43.

Claim 32 is amended to delete the recitation "NORF gene" and to refer instead to "an open reading frame of a *Saccharomyces cerevisiae* genome, wherein the genome is shown in SEQ ID NOS:12,204-12,219, wherein the open reading frame comprises a SAGE tag as shown in SEQ ID NOS:67-811." Dependent claim 43 also is amended to delete the recitation "NORF gene" and to correspond to the amendment made to claim 32. As discussed above in response to the rejection under 35 U.S.C. § 112, paragraph 1, the specification describes the recited open reading frames of the particular recited organism, *Saccharomyces cerevisiae*. Thus, recitation of these open reading frames is definite.



(b) and (f) The term "NORF gene" in claims 32 and 33 is said to be vague and

the metes and bounds of any particular NORF gene are not disclosed or set. The same objection is made to the recitation "NORF genes" in claim 43.

As discussed above, claims 32 and 43 have been amended to delete the recitation "NORF gene." Claim 33 also has been amended to delete this recitation.

(c) The recitation in claim 33 of "involved in" is said to be vague and indefinite because the application does not disclose how to distinguish an involved gene from an uninvolved gene.

Claim 33 is amended to delete the recitation "involved in" and to recite that the open reading frame is "differentially expressed during the cell cycle." Differential expression is defined in the specification at page 6, lines 25-27: "Differentially expressed yeast genes are those whose expression varies by a statistically significant difference (to greater than 95% confidence level) within different growth phases, particularly log phase, S phase, and G2/M."

(d) The recitation of "NORF No. 1, 2, 4, 5, 6, 17, 25, and 27" in claim 34 is said to be vague, indefinite, and incomplete because the application does not disclose the structure of any one of the NORFs.

The recitation "NORF No. 1, 2, 4, 5, 6, 17, 25, and 27" has been deleted from claim 34. Amended claim 34 now recites the open reading frame in amended claim 32. As discussed above, this recitation is definite.

(e) The recitation of "of distinct sequence" in claims 35, 36, and 37 is said to be vague and indefinite because the specification does not indicate from what each of the sequences are distinct and does not distinguish a distinct sequence from an indistinct sequence.

The phrase "of distinct sequence" means that each of the probes in a claimed array has a

sequence that is different from the sequence of each of the other probes in the array. Claims 35, 36, and 37 have been amended to clarify this meaning.

(h) The recitation "said probes" in claim 44 is said to be incomplete because there is no antecedent basis for the recitation.

Claim 44 has been amended to recite that "the at least one probe of each of the open reading frames comprises a SAGE tag." Claim 43 provides antecedent basis for this recitation.

Applicants believe the amended claims are definite. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 103(a)

Claims 32-37, 43, and 44 stand rejected under 35 U.S.C. § 103(a) as obvious over Goffeau *et al.* (*Science* 274, 546, 1996) in view of Velculescu *et al.* (*Science* 270, 484, 1995). Applicants respectfully traverse this rejection.

Goffeau *et al.* is cited as disclosing the entire genome of *Saccharomyces cerevisiae*. Velculescu *et al.* is cited as disclosing analysis of DNA by attaching DNA probes to a solid support. The Office Action asserts it would have been obvious for the ordinary artisan to have combined the teachings of these two references and to have attached the DNAs of Goffeau *et al.* to the solid support of Velculescu *et al.* in order to analyze nucleic acid sequences in *Saccharomyces cerevisiae*.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness based on this combination of references. In particular, the combined references must teach or suggest all the claim limitations (M.P.E.P. § 706.02(j)). Moreover, the motivation to combine the cited references must be found in the references themselves or in the prior art. *Id.*

The limitations of claims 32-37, 43, and 44 are as follows. Each of the claimed arrays must comprise at least one probe that comprises at least 14 nucleotides of a particular open reading frame of a *Saccharomyces cerevisiae* genome. The open reading frame comprises a SAGE tag shown in SEQ ID NOS:67-811. Each of the claimed probe arrays must be present "on a solid support."

First, none of the expressed open reading frames recited in claims 32-37, 43, and 44 are taught or suggested in either Goffeau *et al.* or Velculescu *et al.* In fact, the NORFs taught in the present specification were not even predicted to exist by previous analyses of the yeast genome. The open reading frames which Applicants refer to as "NORFS" ("not previously assigned open reading frames," page 6, line 20) are disclosed only in the present specification, not in the cited prior art.

Second, the specification teaches that the purpose of attaching an array of DNA probes to a solid support is to detect gene expression, *i.e.*, to hybridize mRNA (*e.g.*, page 8, lines 28). Velculescu *et al.* does not teach attachment of DNA to a solid support for the purpose of detecting gene expression. Velculescu *et al.* discloses the technique known as "SAGE" (Serial Analysis of Gene Expression). The only teaching in Velculescu *et al.* of DNA attached to a solid support is at page 484, column 3, lines 10-12, where isolation of the most 3' portion of anchoring enzyme-cleaved cDNA is carried out by binding to streptavidin beads. This teaching would not have motivated an ordinary artisan to have placed DNA of *Saccharomyces cerevisiae* on a solid support to analyze gene expression.

Moreover, to analyze gene expression, *i.e.*, to detect *S. cerevisiae* mRNA, the DNA probes on the solid support must be capable of hybridizing to mRNA transcribed from expressed genes. The skilled artisan would therefore not attach "any of the DNAs" of the *S. cerevisiae*

genome to a solid support, but would attach probes which were known to be capable of hybridizing to mRNA, *i.e.*, probes from the elucidated open reading frames of the *S. cerevisiae* genome. As pointed out above, however, the open reading frames recited in claims 32-37, 43, and 44 were not previously known to be expressed.

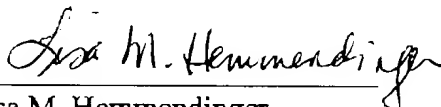
The combination of Goffeau *et al.* and Velculescu *et al.* does not teach or suggest all the limitations of claims 32-37, 43, or 44, nor would the ordinary artisan have been motivated to combine these references. Thus, the Patent Office has failed to carry its burden of establishing that claims 32-37, 43, or 44 are *prima facie* obvious based on the cited references.

Applicants respectfully request withdrawal of this rejection of claims 32-37, 43, and 44 under 35 U.S.C. § 103(a).

Respectfully submitted,

Date: April 10, 2001

By:

  
Lisa M. Hemmendinger  
Registration No. 42,653

Banner & Witcoff, Ltd.  
1001 G Street, N.W.  
Eleventh Floor  
Washington, D.C. 20001-4597  
(202) 508-9100

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Lisa M. Hemmendinger

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Appendix 1. Version of Amendments to the Claims with Markings to Show Changes Made

32. An array of probes on a solid support for detecting gene expression, wherein at least one probe comprises at least 14 contiguous nucleotides of an open reading frame of a *Saccharomyces cerevisiae*, wherein the *Saccharomyces* genome is shown in SEQ ID NOS:12,204-12,219, wherein the open reading frame comprises [a NORF gene comprising] a SAGE tag as shown in SEQ ID NOS:67-811.

33. The array of claim 32 wherein the open reading frame [at least one NORF gene] is differentially expressed during the cell cycle [involved in cell cycle progression].

34. The array of claim 32 wherein the open reading frame comprises a SAGE tag [NORF gene is] selected from the group consisting of SEQ ID NOS:67, 68, 70, 71, 72, 83, 91, and 93 [NORF No. 1, 2, 4, 5, 6, 17, 25, and 27].

35. The array of claim 32 which comprises at least 100 probes, wherein each probe has a sequence that is different from each other sequence [of distinct sequence].

36. The array of claim 32 which comprises at least 500 probes, wherein each probe has a sequence that is different from each other sequence [of distinct sequence].

37. The array of claim 32 which comprises at least 1,000 probes, wherein each probe has a sequence that is different from each other sequence [of distinct sequence].

43. The array of claim 32 which comprises at least one probe comprising at least 14 contiguous nucleotides of each of the open reading frames [NORF genes] identified by the SAGE tags shown in SEQ ID NOS:67-811.

44. The array of claim 43 wherein the at least one probe of each of the open reading frames comprises a SAGE tag [said probes comprise said SAGE tags].

Appendix 2. Version of Amendments to the Specification with Markings to Show  
Changes Made

Page 15, line 23, to page 16, line 2:

A comprehensive analysis for NORF genes was performed using the SAGE data. Yeast genome intergenic regions were defined as regions outside annotated ORFs or the 500bp region downstream of annotated ORFs (yeast genome sequence and tables of annotated ORFs were obtained from SGD at the Stanford Saccharomyces genome website) [<http://genome-www.stanford.edu/Saccharomyces/>]. Based on sequence analysis a total of 9524 putative ORFs of 25-99 amino acids were present in the intergenic regions; 510 of these ORFs contain or are adjacent to observed SAGE tags (Table 6). Of the 60,633 SAGE tags analyzed, there were 302 unique SAGE tags either within or adjacent to intergenic ORFs (100bp upstream or 500bp downstream of the ORF) (Table 6). Note that in some cases, more than one NORF contains or is adjacent to the SAGE tag. These tags matched the genome uniquely, were in the correct orientation, and were expressed at levels greater than 0.3 transcript copies per cell.

Page 19, line 26, to page 20, line 8:

As very sparse data are available for yeast mRNA sequences and efforts to date have not been able to identify a highly conserved polyadenylation signal (Imniger and Braus, 1994; Zaret and Sherman, 1982), we used 14 bp of SAGE tags (i.e. the NlaIII site plus the adjacent 10 bp) to search the yeast genome directly (yeast genome sequence obtained from the Stanford yeast genome ftp site [[genome-ftp.stanford.edu](http://genome-ftp.stanford.edu)]) on August 7, 1996, SEQ ID NOS:812-827). Because only coding regions are annotated in the yeast genome, and SAGE tags can be derived

from 3' untranslated regions of genes, a SAGE tag was considered to correspond to a particular gene if it matched the ORF or the region 500 bp 3' of the ORF (locus names, gene names and ORF chromosomal coordinates were obtained from Stanford yeast genome ftp site, and ORF descriptions were obtained from MIPS www site [<http://www.mips.biochem.mpg.de/>] on August 14, 1996). ORFs were considered genes with known functions if they were associated with a three letter gene name, while ORFs without such designations were considered uncharacterized.



## PATENT

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
VELCULESCU <i>et al.</i>	)	Group Art Unit: 1633
Serial No. 09/012,031	)	Examiner: J. Martinell
Filed: January 22, 1998	)	Atty. Docket No. 01107.73251

For: CHARACTERIZATION OF THE YEAST TRANSCRIPTOME

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents  
Washington, D.C. 20231

Sir:

I, VICTOR VELCULESCU, declare as follows:

1. I am named as a co-inventor of the subject matter disclosed and claimed in the patent application identified above. The following statements are based on either personal knowledge or information and belief.

2. On August 7, 1996, I transferred 16 files from the Stanford yeast genome ftp site (genome-ftp.stanford.edu) to the computer network at the Johns Hopkins University School of Medicine, Baltimore, MD, via a computer terminal located at the Molecular Genetics Laboratory at the University. Each of the 16 files contained the entire nucleotide sequence of one of the chromosomes in the genome of the yeast *Saccharomyces cerevisiae* (one chromosome per file). The *Saccharomyces cerevisiae* genome contains 16 chromosomes (*see Goffeau et al., Science* 274, 546, 1996, which is of record in this application).

3. Since August 7, 1996, the 16 transferred files have been stored on the computer network at the Johns Hopkins University School of Medicine. I believe the nucleotide sequence in each of these 16 files is identical to the nucleotide sequence which was available for that chromosome of the *Saccharomyces cerevisiae* genome on the Stanford website on August 7, 1996. First, I have not altered the contents of these files. Second, based on my information and belief, no one else has altered the contents of these files. A file list, provided as Exhibit 1, shows that each of the 16 files still bears a date of August 7, 1996. This date indicates that no changes have been made to the contents of any of the 16 files since I downloaded them on August 7, 1996.

4. I copied each of the 16 files to a zip disk and provided the disk to Lisa M. Hemmendinger at Banner & Witcoff, Ltd. for use in preparing a sequence listing for application Serial No. 09/012,02331.

5. The nucleotide sequences which I transferred on August 7, 1996 and which I provided for preparation of the sequence listing are the same nucleotide sequences which we searched using the SAGE tags disclosed in Tables 3 and 4 of application Serial No. 09/012,031. These searches identified the NORFs (not previously assigned open reading frames) which are disclosed in application Serial No. 09/012,031.

6. I declare that all statements made herein of my own knowledge are true and that I believe all statements made on information and belief are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

3/06/00

Date



Victor Velculescu, M.D., Ph.D.

